REMARKS/ARGUMENTS

The Invention

The invention pertains to a composition comprising an interleukin-2 receptor associated polypeptide, wherein the polypeptide is capable of forming a complex with the monoclonal antibody produced by the hybridoma PTA-82, has a molecular weight of about 32-34 kDa or 26-28 kDa as determined by SDS-PAGE, and is expressed by Kit-225 cells or HuT 102 cells, and methods of purifying the same.

The Pending Claims

Claims 1, 3, 5, 9, 11-15, and 22-29 are pending. Claims 1, 3, 5, and 22-29 are directed to compositions comprising interleukin-2 receptor associated polypeptides, which are capable of forming a complex with monoclonal antibodies produced by the hybridoma PTA-82, have a molecular weight of about 32-34 kDa or 26-28 kDa as determined by SDS-PAGE, and are expressed by Kit-225 cells or HuT 102 cells. Claims 9 and 11-14 are directed to methods of purifying the subject interleukin-2 receptor associated polypeptides. Claim 15 is directed to a composition comprising the interleukin-2 receptor associated polypeptide purified by the method of claim 9.

The Office Action

Claims 1, 3, 5, 9, 11-15, and 22-29 are rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. Claims 1, 3, 5, 9, 13-15, and 22-29 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as allegedly obvious over Colamonici et al. (*J. Immunol.*, *145*, 155-160 (1990)) ("the Colamonici reference"). Reconsideration of these rejections is respectfully requested.

Examiner Interview

Applicants wish to thank Examiner Jiang for the courtesy extended during the telephonic interview of August 10, 2006, with Applicants' representatives Heather Kissling and Mojdeh Bahar. Applicants are most appreciative of the Examiner's time in discussing the rejections outlined herein. The remarks set forth herein generally reflect the substance of

Applicants' position conveyed to the Examiner by Applicants' representatives during the telephone interview.

Discussion of the Rejection Under 35 U.S.C. § 112, First Paragraph

The Office contends that claims 1, 3, 5, 9, 11-15, and 22-29 allegedly contain subject matter that is not described in the specification in such a way so as to enable an ordinarily skilled artisan to make and use the invention. This rejection is respectfully traversed.

The Office contends that the specification lacks evidence demonstrating that the claimed polypeptides associate with the interleukin-2 receptor (IL-2R) and, therefore, that an ordinarily skilled artisan cannot make and use the invention. Contrary to the Office's assertions, the specification provides ample evidence demonstrating that the claimed polypeptides associate with IL-2R. As described in the specification, the claimed interleukin-2 receptor associated polypeptides (ILRAPs) were immunoprecipitated with the 5F7 antibody, which is specific to ILRAPs and does not react immunologically with the α, β, or γ subunits of IL-2R in a direct fashion (see, e.g., page 27, lines 7-10; and page 37, lines 28-31). The 5F7 antibody also co-immunoprecipitated IL-2R, which strongly suggests that the ILRAPs were associated with the IL-2R (see specification at, e.g., page 37, lines 28-31).

Likewise, Example 5 of the specification describes receptor internalization assays that established that ILRAPs are associated with IL-2R. Addition of IL-2 to IL-2R-bearing cells triggers uptake and internalization of IL-2R and associated proteins. Addition of IL-2 to Kit-225 cells at 37° C prompted a major reduction in the surface expression of IL-2Rβ and ILRAP, i.e., ILRAP was internalized with IL-2Rβ (see specification at, e.g., page 33, line 11-21; and page 38, lines 5-17). In contrast, ILRAP levels did not change when IL-2 was added to Kit-225 cells at 4° C, a temperature at which IL-2R internalization is blocked (see specification at, e.g., page 38, lines 5-17). Example 6 of the specification states that flow cytometric resonance energy transfer (FRET) verified that ILRAP and IL-2Rα are non-randomly associated on the surface of T-cell lines (see specification at, e.g., page 39, lines 3-5; and Figure 5). The specification clearly establishes that the claimed polypeptides associate with IL-2R. Furthermore, the specification provides adequate guidance to allow the ordinarily skilled artisan to determine if a putative ILRAP associates with IL-2R using, for example, the methods described in Examples 3-6.

The Office cites Applicants' declaration under 37 C.F.R. § 1.137 of Thomas Waldmann, M.D., submitted on March 17, 2006, as suggesting that the claimed ILRAPs are not associated with IL-2R. According to the Office, the data demonstrate that the anti-Tac antibody fails to remove ILRAPs from Kit-225 cell lysates. The Office concludes from the data that the claimed polypeptides are not associated with IL-2Rα. The premise underlying the Office's conclusion is flawed; not all IL-2Rα-associated proteins are immunoprecipitated with all anti-IL-2Rα antibodies. Failure of the anti-Tac antibody to immunoprecipitate ILRAP is not predictive of whether ILRAPs associate with IL-2R.

Despite the general nature of the antibody's name, the anti-Tac antibody referred to in the declaration and the Colamonici reference is a specific monoclonal antibody that binds to IL-2Rα (see, e.g., the Colamonici reference at page 155, column 2, paragraph 2). The anti-Tac antibody does not immunoprecipitate every IL-2R associated peptide. Indeed, the anti-Tac antibody fails to immunoprecipitate a protein described by the Colamonici reference as associated with IL-2Rα. The Colamonici reference teaches that ICAM-1 is closely associated with the Tac protein (i.e., IL-R2α) (the Colamonici reference at, e.g., page 158, paragraph bridging columns 1 and 2). However, the anti-Tac antibody does not co-immunoprecipitate ICAM-1 with the Tac protein (see, e.g., Szollosi et al., *PNAS USA*, *84*, 7246-7250 (1987), submitted herewith).

In addition, like the ILRAPs of the invention, Class I major histocompatibility complex (MHC) and Class II MHC are non-randomly associated with IL-2Rα (see, for example, Vereb et al., *PNAS USA*, *97*(11), 6013-6018 (2000); and Matko et al., *Eur. J. Biochem.*, *269*, 1199-1208 (2002), submitted herewith). Indeed, several different biophysical techniques, including FRET, cross-correlation microscopy, and confocal microscopy, reveal that Class I MHC and Class II MHC associate with IL-2Rα (see, e.g., the Vereb reference at paragraph bridging pages 1201-1202, through page 1202, column 1, paragraph 2, and paragraph bridging pages 1024-1205, through page 1205, column 1, paragraph 1; and the Matko reference at page 6016, column 1, paragraph 2, through page 6017, paragraph bridging columns 1 and 2). Yet, neither Class I MHC β2 microglobulin nor Class II MHC was immunoprecipitated by Colamonici et al. using the anti-IL-2Rα antibody, 7G7/B6. The proteins also were not identified by Colamonici's IL-2 cross-linking assays. The Colamonici

reference only identifies proteins corresponding to SDS-PAGE gel bands of 95-100 kDa, 75 kDa, 55 kDa, 42 kDa, 37 kDa, and 20 kDa (see, e.g., the Colamonici reference, "Discussion" section). Class I MHC β2 microglobulin has a molecular weight of 12 kDa (see, e.g., Lewis and Elliot, *Current Biology*, *8*, 717-720 (1998), "Abstract" section). Class II MHC has a molecular weight of 59-62 kDa (Fundamental Immunology, 2d edition, William Paul Ed., Raven Press, 1989). Thus, the immunoprecipitation assays using anti-IL-2Rα antibodies described in the Colamonici reference did not immunoprecipitate molecules proven to be associated with IL-2Rα.

In view of the above, the specification provides ample evidence that the claimed ILRAPs associate with IL-2Rα. The data submitted by Applicants during prosecution do not refute the specification's disclosure regarding the association of ILRAPs and IL-2R. Furthermore, an ordinarily skilled artisan can make and use the invention as claimed using the specification as a guide. Accordingly, Applicants respectfully request withdrawal of the rejection of claims 1, 3, 5, 9, 11-15, and 22-29 under Section 112, first paragraph.

Discussion of Rejections Under 35 U.S.C. §§ 102(b) and 103(a)

Claims 1, 3-5, 9, 13-15, and 22-29 are rejected under Section 102(b) as allegedly anticipated by or, in the alternative, under Section 103(a) as allegedly obvious in view of, the Colamonici reference. These rejections are traversed for the reasons set forth below.

Regarding the Section 102 rejection, the Office bears the burden of presenting at least a prima facie case of anticipation. *In re King*, 801 F.2d 1324, 1327 (Fed. Cir. 1987). The burden of going forward then shifts to the applicant to present rebuttal evidence. *Id.* Once an applicant provides arguments and evidence in support of patentability, an examiner "must step back and consider anew the question of whether the claims are properly rejected having weighed the evidence and arguments made of record in support of patentability against those in support of unpatentability." *Ex Parte Jones*, 2001 WL 1057381 (B.P.A.I. 2001) (citing *In re Hedges*, 783 F.2d 1038, 1039 (Fed. Cir. 1986); *In re Piasecki*, 745 F.2d 1468, 1471 (Fed. Cir. 1984); *In re Rinehart*, 531 F.2d 1048, 1052 (C.C.P.A. 1976)). Here, Applicants presented rebuttal arguments and evidence demonstrating that the proteins identified in the Colamonici reference physically differ from those of the pending claims in at least three respects. The Office has refused to "step back" and consider the patentability of the claims in

view of the totality of the evidence submitted by the applicants. While the evidence concerning each physical characteristic, alone, distinguishes the Colamonici proteins from the polypeptide of the invention, the evidence *taken as a whole* clearly rebuts the Office's alleged prima facie case.

First, the Colamonici reference does not disclose IL-2R associated polypeptides having a molecular weight of 32-34 kDa or 26-28 kDa as determined by SDS-PAGE, as required by the pending claims. Instead, the Colamonici reference discloses a 37 kDa protein and a 20 kDa protein identified in HuT 102 cells, MT-1 cells, and MLA-144 cells. In other words, the Colamonici reference discloses a protein having a *3-5 kDa* molecular weight difference compared to the IL-2R associated protein of claim 1, and a protein having a *6-8 kDa* difference in molecular weight compared to the protein of claim 3. Despite the fact that the Colamonici reference does not teach or suggest a protein having the molecular weight range required by the pending claims, the Office contends that the Colamonici reference anticipates the claimed invention because the differences in molecular weights *could* be due to experimental conditions. As set forth in paragraphs 2 and 3 of the Declaration under 37 C.F.R. § 1.132 of Richard Bamford, Ph.D., submitted herewith, 3-8 kDa differences in molecular weight of 20-40 kDa proteins is significant. The significant differences in molecular weight lead to the conclusion that the Colamonici reference does not disclose an ILRAP of 32-34 kDa or 26-28 kDa (see Rule 132 Declaration of Richard Bamford, Ph.D., paragraphs 2 and 3). The Office has failed to address this deficiency of the Colamonici reference with anything but unsupported, conclusory statements.

Moreover, not only does the Colamonici reference fail to disclose a polypeptide with the molecular weight required by claims 1 and 3, the Colamonici reference fails to disclose an IL-2R associated polypeptide that binds to an antibody produced by the hybridoma PTA-82, e.g., the 5F7 antibody. In the Declaration under 37 C.F.R. § 1.132 of Thomas Waldmann, M.D., submitted on March 17, 2006, Applicants demonstrated that the 37 kDa protein of the Colamonici reference is not capable of forming a complex with a monoclonal antibody produced by the PTA-82 hybridoma. The Colamonici reference teaches that the 37 kDa protein is present on MLA-144 cells (the Colamonici reference, paragraph bridging pages 159-160). Applicants contacted MLA-144 cells with the 5F7 monoclonal antibody, which is produced by the PTA-82 hybridoma (Rule 132 Declaration of Thomas Waldmann, M.D.,

paragraph 9; and Example 1 of the specification). The 37 kDa protein failed to form a complex with the 5F7 antibody, as determined by flow cytometry (Rule 132 Declaration of Thomas Waldmann, M.D., paragraph 9 and Exhibit 4). Based on these results, it is reasonable to predict that the 37 kDa protein identified in the Colamonici reference on HuT 102 cells also does not form a complex with a monoclonal antibody produced by the PTA-82 hybridoma, as required by the pending claims (Rule 132 Declaration of Richard Bamford, Ph.D., paragraphs 4 and 5).

Furthermore, Applicants submitted additional evidence that distinguishes the proteins described in the Colamonici reference from the ILRAPs of the pending claims. The Colamonici reference characterizes the disclosed 37 kDa and 20 kDa proteins as immunoprecipitated with the anti-Tac antibody (the Colamonici reference, paragraph bridging pages 159-160). In other words, one of the distinguishing characteristics of the 37 kDa and 20 kDa proteins is the ability to form a complex with the anti-Tac antibody such that the proteins are removed from cellular lysates via immunoprecipitation. In the Rule 132 Declaration of Thomas Waldmann, M.D., submitted on March 17, 2006, Applicants demonstrated that the claimed ILRAPs do not have this distinguishing characteristic. Applicants removed from Kit-225 lysates IL-2R associated proteins that form complexes with the anti-Tac antibody (Rule 132 Declaration of Thomas Waldmann, M.D., paragraph 8). As such, Applicants removed via immunoprecipitation the 37 kDa and 20 kDa identified by the Colamonici reference (Rule 132 Declaration of Thomas Waldmann, M.D., paragraph 8 and Exhibit 3, compare lanes 3 and 6). The remaining lysate was then contacted with the 5F7 antibody, and any ILRAPs that form a complex with the 5F7 antibody were immunoprecipitated (Rule 132 Declaration of Thomas Waldmann, M.D., paragraph 8). As seen in lane 8 of Exhibit 4 submitted with the Rule 132 Declaration, the inventive ILRAPs remained after preclearance of Colamonici's 37 kDa and 20 kDa proteins, i.e., the claimed polypeptides *cannot* be the proteins identified in the Colamonici reference. Although the experiment employed Kit-225 cells, the results are reasonably predictive of results that would be achieved in HuT 102 cells (Rule 132 Declaration of Richard Bamford, Ph.D., paragraph 7). Therefore, Applicants distinguished the claimed ILRAPs from the proteins of the Colamonici reference based on physical characteristics disclosed in the reference.

Applicants have submitted arguments and scientific reasoning and evidence that rebut the Office's assertion that the Colamonici reference discloses the ILRAPs of the pending claims. The Office is now required to "step back" and consider the totality of the evidence provided by Applicants concerning the patentability of the claimed subject matter. Applicants have distinguished the claimed polypeptides from those of the prior art based on three physical characteristics. Taken as a whole, the experimental data provided by Applicants clearly demonstrate that the Colamonici reference does not disclose an ILRAP capable of forming a complex with the monoclonal antibody produced by the hybridoma PTA-82, having a molecular weight of about 32-34 kDa or 26-28 kDa as determined by SDS-PAGE, and expressed by Kit-225 cells or HuT 102 cells, as required by the pending claims. As such, the Section 102 rejection of claims 1, 3-5, and 22-25 should be withdrawn.

Furthermore, the Colamonici reference does not teach or suggest the method of claims 9, 13, and 14, or the resulting composition of claim 15. The claimed method for purifying an ILRAP comprises contacting a cell extract with an anti-ILRAP antibody, wherein the antibody forms a complex with the ILRAP. The Colamonici reference does not disclose such an antibody. The 37 kDa and 20 kDa proteins identified in the Colamonici reference were immunoprecipitated with the anti-Tac monoclonal antibody and the 7G7/B6 monoclonal antibody, both of which are specific for the Tac protein (the Colamonici reference at page 155, column 2, paragraph 2). The Colamonici reference does not describe an anti-ILRAP antibody, a method of purifying ILRAPs using such antibodies, or a composition comprising an ILRAP purified by such a method. Because the Colamonici reference does not teach each and every feature of the claimed method and resulting composition, the Section 102 rejection of claims 9 and 13-15 is improper and should be withdrawn.

The Colamonici reference also does not render obvious the subject matter of the pending claims. As discussed above, the Colamonici reference does not disclose or suggest an IL-2 receptor associated protein that is capable of forming a complex with the monoclonal antibody produced by the hybridoma PTA-82, let alone such an IL-2 receptor associated polypeptide that has a molecular weight of about 32-34 kDa or about 26-28 kDa. Furthermore, the Colamonici reference does not disclose or suggest a method of purifying an ILRAP using an anti-ILRAP antibody. In view of these deficiencies of the Colamonici reference, one of ordinary skill in the art would not be led to modify the disclosure of the

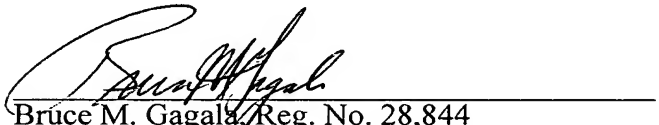
Colamonici reference in a way so as to arrive at the claimed invention. Accordingly, the Section 103 rejection of the pending claims should be withdrawn.

For the foregoing reasons, the Colamonici reference does not teach or suggest the subject matter of the claimed invention. Applicants respectfully request withdrawal of the rejections under Sections 102 and 103.

Conclusion

Applicants respectfully submit that the patent application is in condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,



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